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NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 03 October 2000 (03.10.00)	
International application No. PCT/NL00/00108	Applicant's or agent's file reference P48241PC00
International filing date (day/month/year) 21 February 2000 (21.02.00)	Priority date (day/month/year) 19 February 1999 (19.02.99)
Applicant HENNINK, Wilhelmus, Everhardus et al	

1. The designated Office is hereby notified of its election made:



in the demand filed with the International Preliminary Examining Authority on:

22 August 2000 (22.08.00)



in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Pascal Piriou

Telephone No.: (41-22) 338.83.38

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference P48241PC00	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/NL 00/ 00108	International filing date (day/month/year) 21/02/2000	(Earliest) Priority Date (day/month/year) 19/02/1999
Applicant UNIVERSITY UTRECHT et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NL 00/00108

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 3,8-10,18,20 (in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 3,8-10,18,20 (in part)

Present claims 3,8-10,18 relate to a product defined by reference to a desirable characteristic or property, namely "substantial part" (claim 3), "sufficiently low..." (claims 8,10), "sufficiently high ..." (claim 9), to physically link..." (claim 18). The claims cover all products having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the products reported in the examples and as defined in claims 11 and 12, resp. Moreover, the wording of claim 20 is not clear, either, and has therefore been interpreted in the light of the description (page 16, lines 16-24).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

National Application No

PCT/NL 00/00108

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/22 A61K47/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 99 36100 A (EFRAT BIOPOLYMERS LTD ; ZEHAVI ZEEV (IL); DOMB AVRAHAM J (IL)) 22 July 1999 (1999-07-22) * see in particular page 5, line 8 - page 9, line 16; examples 9-11 *	1,2,6,7, 13,19, 21-23
A	WO 98 00170 A (UNIV UTRECHT ; DIJK WOLTHUIS WENDELMOED NELLE (NL); HENNINK WILHELM) 8 January 1998 (1998-01-08) cited in the application *see in particular examples 3,6 * --- -/--	1-23



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

27 June 2000

Date of mailing of the international search report

14. 07. 00

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Isert, B

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/NL 00/00108

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>JONG DE S J ET AL: "MONODISPERSE ENANTIOMERIC LACTIC ACID OLIGOMERS: PREPARATION, CHARACTERIZATION, AND STEREOCOMPLEX FORMATION" MACROMOLECULES, vol. 31, no. 19, 22 September 1998 (1998-09-22), pages 6397-6402, XP000778163 ISSN: 0024-9297 * see in particular abstract and introduction (page 6397) *</p>	1-23
A	<p>OKIHARA ET AL.: "Crystal Structure of stereocomplex of poly(L-lactide) and poly(D-lactide)" J. MACROMOLECUL. SCI.- PHYS., vol. B30, no. 1&2, 1991, pages 119-140, XP000915604 cited in the application *see the abstract; & page 120 (introduction) *</p>	3-5
P,A	<p>DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US DE JONG, S. J. ET AL: "Stereocomplex formation in enantiomeric lactic acid oligomers" retrieved from STN Database accession no. 132:180789 XP002141115 abstract & PROC. INT. SYMP. CONTROLLED RELEASE BIOACT. MATER. (1999), 26TH, 691-692 ,</p>	1-23
T	<p>DE JONG ET AL.: "Novel self-assembled hydrogels by stereocomplex formation in aqueous solution of enantiomeric lactic acid oligomers grafted to dextran" MACROMOLECULES, vol. 33, no. 10, March 2000 (2000-03), pages 3680-3686, XP000915595</p>	

INTERNATIONAL SEARCH REPORT

on patent family members

ional Application No

PCT/NL 00/00108

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9936100	A	22-07-1999	AU	1888999 A	02-08-1999
			EP	0967998 A	05-01-2000
WO 9800170	A	08-01-1998	AU	3360197 A	21-01-1998
			EP	0910412 A	28-04-1999
			AU	5069798 A	10-06-1998
			EP	0941068 A	15-09-1999
			WO	9822093 A	28-05-1998

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P48241PC00	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/NL00/00108	International filing date (day/month/year) 21/02/2000	Priority date (day/month/year) 19/02/1999
International Patent Classification (IPC) or national classification and IPC A61K9/22		
Applicant UNIVERSITEIT UTRECHT et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 7 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☒ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 22/08/2000	Date of completion of this report 19.02.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Isert, B Telephone No. +49 89 2399 8691 

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NL00/00108

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:

Description, pages:

1-42 as originally filed

Claims, No.:

1-23 as originally filed

Drawings, sheets:

1/11-11/11 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/NL00/00108

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 3,8-10, 18, 20 (in part).

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NL00/00108

could be formed.

☒ no international search report has been established for the said claims Nos. 3,8-10, 18, 20 (in part).

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 1-23
	No: Claims

Inventive step (IS)	Yes: Claims 1-23
	No: Claims

Industrial applicability (IA)	Yes: Claims 1-23
	No: Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/NL00/00108

SECTION II

- 1). The priority document EP99200472 does not comprise the subject-matter of present claims 3-5, 17, description pages 13 (line 15) - page 16 (line 12), page 17 (lines 10-30), page 18 (lines 16-23); pages 25-52; and Figures 1/11 & 4/11-11/11.

SECTION III

- 2). Claims 3, 8-10, 18, 20 are examined on matter which has been searched. See the remarks made on form PCT/ISA/210.

SECTION V:

- 3). The following documents (D) cited in the International search report are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1 = WO-A-9936100

D2 = WO-A-9800170 (also cited in the application)

D3 = Macromolecules, 1998, 31(19): 6397-6402

D4 = J. Macromol. Sci.-Phys., 1991, B30(1&2): 119-140
(also cited in the application)

D5 = Chemical Abstracts (as STN HCAP abstract) 132:180789, &Proc. Int. Symp. Control. Bioact. Mater., July 1999, 26: 691-692

D6 = Macromolecules, 2000, 33(10): 3680-3686

Unless indicated otherwise reference is made to the relevant passages emphasized in the search report.

- 3.1 The documents D5 and D6 (representing the scientific disclosure of the present application) have been published after the priority dates thereof.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/NL00/00108

- 3.2 The intermediate document D1 relates to stereocomplex hydrogels formed of monomers of an opposite chirality which are present on the same or a second polymer chain. See also the present application at page 7, lines 3-8. However, the hydrogels of D1 differ from those described in the present application in the average degree of substitution and the average chain length. See present claims 11 and 12.

4). Novelty

None of the documents D2 -D4 describe the present stereocomplex hydrogels.

5). Inventive step:

The subject-matter of the claims is considered to involve an inventive step:

The present hydrogels provide a controlled release system for protein drugs, cf. page 4, lines 16-34 of the description.

It is known from the D2, eg., that modified dextran hydrogels can be used in this respect. The present hydrogels differ from those described in D2 in that a mixture of dextrans grafted with oligomeric groups of opposite chirality is used. This particular modification is said to avoid the use of the bio-incompatible crosslinkers required in D2, cf. page 4, lines 10-17 of the present description. Thus, the problem underlying the present application could be the provision of a biocompatible, non-toxic protein release system on the basis of dextran hydrogels. The problem has been solved: The controlled release is shown in example 5, and the materials used indicated that there is reduction in toxicity.

Enantiomeric polylactic oligomers are available from D3 and D4, however, there is no pointer in said documents suggesting a potential use in pharmaceutical hydrogels.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/NL00/00108

6). Industrial applicability

The pharmaceutical compositions of claims 1-23 are considered industrially applicable under Article 33 (4) PCT.

SECTION VI

D1 = WO-A-9950042, publication date 22.07.99, filing date 14.01.99, priority date 14.01.98

SECTION VII

- 7). Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D3 is not mentioned in the description, nor are these documents identified therein.

SECTION VIII

- 8). The terms "sufficiently low..." (claims 8,10), "sufficiently high ..." (claim 9), to physically link..." (claim 18) attempt to define the invention by the result to be achieved, and should be replaced by the precise definitions found eg., in claims 11 and 12.
- 9). The definition of the use according to claim 20 ("use of mixture ... ex vivo to form a hydrogel ... in vivo") is unclear, and should be elucidated to be in line with the description at page 16, lines 16-24.
- 10). The term "substantial part" used in claim 3 is unclear and should be clarified in the light of the examples, e.g.